Claims

1. Process for the synthesis of isobutyl methyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridine dicarboxylate (Nisoldipine) comprising the reaction of isobutyl 2-(2-nitrobenzylidene)acetoacetate with methyl 3-aminocrotonate, added to the reaction mixture in a single portion or portionwise in an apolar solvent, to give crude Nisoldipine.

2. The process as claimed in claim 1, wherein the apolar solvent is selected from the group consisting of aliphatic or cycloaliphatic solvents.

3. The process as claimed in claim 2, wherein the solvent is selected from the group consisting of cyclohexane and n-hexane.

4. The process as claimed in claim 1, wherein the reaction of isobutyl 2-(2-nitrobenzylidene)acetoacetate and methyl 3-aminocrotonate is carried out in the presence of 4-dimethylaminopyridine.

5. The process as claimed in claim 1, wherein, after the reaction of isobutyl 2-(2-nitrobenzylidene)acetoacetate with methyl 3-aminocrotonate in an apolar solvent to give crude Nisoldipine, said Nisoldipine is purified by crystallisation from a water/water soluble solvent mixture to give a pure Nisoldipine final product.

6. The process as claimed in claim 5, wherein the water/water soluble solvent mixture is water/acetone.

7. The process as claimed in claim 1, wherein, before reaction of isobutyl 2-(2-nitrobenzylidene)acetoacetate with methyl 3-aminocrotonate, said Nisoldipine synthesis intermediate, i.e. isobutyl 2-(2-nitrobenzylidene)acetoacetate, is obtained by reacting 2-nitrobenzaldehyde with isobutyl acetoacetate in methylene chloride, as solvent, in the presence of a catalytic amount of piperidine formate at a temperature of -10°C to 50°C.

8. The process as claimed in claim 7, wherein the reaction of 2-nitrobenzaldehyde with isobutyl acetoacetate is carried out at a temperature of 20°-50°C.

9.The process a claimed in claim 8, wherein the temperature ranges from 27° to 33°C.

10. The process a claimed in claim 7, wherein the catalyst, piperidine formate, forms in situ in the reaction mixture by addition of equimolar amounts of formic acid and piperidine.

11. The process as claimed in claim 7, wherein the amount of catalyst, piperidine formate, used is 0.05-0.7 mol catalyst/mol 2-nitrobenzaldehyde.

12. The process as claimed in claim 11, wherein the amount of catalyst is 0.05-0.6 mol catalyst/mol 2-nitrobenzaldehyde.

13. The process as claimed in claim 12, wherein the amount of catalyst is 0.25 mol catalyst/mol 2-nitrobenzaldehyde.

14. The process as claimed in claim 7, wherein isobutyl 2-(2-nitrobenzylidene)acetoacetate is isolated in the presence of aqueous acetic acid as solvent.

15. Process for the synthesis of 2-(2-nitrobenzylidene)acetoacetate including the reaction of 2-nitrobenzaldehyde with isobutyl acetoacetate in metylene chloride, as solvent, in the presence of a catalytic amount of piperidine formate, at a temperature of –10°C to 50°C.

16. The process as claimed in claim 15, wherein the reaction is carried out at temperature ranging from 20° to 50°C.

17. The process as claimed in claim 15, wherein the reaction is carried out at 27°-33°C.

18. The process as claimed in claim 15, wherein the catalyst, piperidine formate, forms in situ in the reaction mixture by addition of equimolar amounts of formic acid and piperidine.

19. The process as claimed in claim 15, wherein the amount of catalyst, piperidine formate, used is 0.05-0.7 mol catalyst/mol 2-nitrobenzaldehyde.

20. The process as claimed in claim 15, wherein the amount of catalyst is 0.05-0.6 mol catalyst/mol 2-nitrobenzaldehyde.

21.The process as claimed in claim 15, wherein the amount of catalyst is 0.25 mol catalyst/mol 2-nitrobenzaldehyde.

22.The process as claimed in claim 15, wherein isobutyl 2-(2-nitrobenzylidene)acetoacetate is isolated in the presence of aqueous acetic acid as solvent.